One of ordinary skill in the art would be aware of the effect that in 5-formyltetrahydrofolic acid solutions citrate may reduce hydrolysis and oxidative cleavage of the basic skeleton and thus reduce the formation of products such as p-aminobenzoylglutamic acid and pterin- and tetrahydropterin derivatives. However this same person surely also knows that 5,10-methylenetetrahydrofolic acid in solution always stays in equilibrium with tetrahydrofolic acid and formaldehyde. Any stabilization of 5,10-methylenetetrahydrofolic acid therefore has to push this equilibrium to the 5,10-methylenetetrahydrofolic acid side in order to gain the stabilization effect desired. However, Applicants could not find even a slight indication in the state of the art that in the claimed basic pH region citrate could inhibit the separation of formaldehyde from 5,10-methylenetetrahydrofolic acid and therefore stabilize 5,10-methylenetetrahydrofolic acid.

It also becomes clear why despite Nijker's teaching in 1995, Odin still describes 3 years later regarding 5,10-methylenetetrahydrofolic acid in CANCER INVESTIGATION, Vol. 16 No. 7, 1998, page 447-455, repeatedly as being highly sensitive to oxidation (see e.g. page 447, Abstracts). Odin states that only a rigorous exclusion of atmospheric oxygen by the use of special technical devices for the reconstitution of solid formulations and the injection of 5,10-methylenetetrahydrofolic acid in an air-free environment can make this substance manageable. This air-free handling is described as being imperative for 5,10-methylenetetrahydrofolic acid (see e.g. page 545, second column, lines 5-7).

Compositions according to the presently claimed invention, however, show a totally different behavior, which are not expected in view of the state of the art.

The Office Action states that it would have been obvious to one skilled in the art at the time of the instantly claimed invention to add citrate to the composition of Odin et al together with adjusting the pH to 8.95. However, there are various techniques described for the stabilization of folates. For example, WO 95/26963 relates to the stabilization of aqueous solutions containing 5-formyltetrahydrofolic acid by the addition of sodium citrate, sodium acetate or sodium chloride. WO 95/26963 even attributes acetate and citrate as having a comparable effect on the stabilisation of 5-formyltetrahydrofolic acid. On the other hand neither acetate, nor oxalate, nor maleate nor salts of other acids have shown any stabilization effect on 5,10-methylenetetrahydrofolic acid. Only citrate in combination with the specific claimed pH rage is effective.

If the Office Action would maintain its position that it would have been obvious to one skilled in the art at the time of the instantly claimed invention to add citrate to the

composition of Odin et al together with adjusting the pH to 8.95, then surely it would follow that the Office Action would also had expected that other salts or different stabilization methods known in this filed (like the addition of ascorbic acid or other a reducing agent) would have the same or similar effect. However that is not the case, and demonstrates the incorrectness of the allegations.

In addition to that if all the knowledge in the field of folates would be transferable from one compound to the other, one would think that, e.g., US 4,931,441, disclosing the use of citrate for the stabilisation of 5-formyltetrahydrofolic acid and referring thereby to an upper pH as being "not higher than 8.5" (see column 2 lines 18-19, column 3 line 5, claim 1, claim 5 and claim 11) must also be followed for 5,10-methylenetetrahydrofolic acid. However used pH values of US 4,931,441 differ remarkably from the preferred pH values of the presently claimed invention. So, US 4,931,441 even teaches away from the presently claimed invention by teaching that a maximal stability is reached at a pH value of 8.1, which is well below the preferred pH value of the presently claimed invention. And even more, US 4,931,441 states that at a pH value of above 8.5 no stable compositions can be obtained.

The Office Action is correct in that the applied parameters under which Odin has disclosed stability indications are different from the parameters applied in the presently claimed invention. However, as can be seen from the earlier provided comparative data, the difference is huge. All data, for lyophilisates and even more for solutions of 5,10-methylenetetrahydrofolic acid show, an against the state of the art remarkably increased stability. This effect is by far more efficient/significant than could ever have been expected. So, even without a reducing agent the compound is showing a reasonable stability for its pharmaceutical use. The currently claimed invention makes it possible for the first time to prepare difficultly soluble calcium or acidic salts of 5,10-methylenetetrahydrofolic acid.

Only based on the knowledge disclosed by the current application it had been possible to develop a pharmaceutically applicable form of the long desired 5,10-methylenetetrahydrofolic acid showing an acceptable stability as a drug product. This development has been started with the US company Biokeys (their drug product has been called CoFactor) and afterwards with the Swedish oncology firm Isofol (drug product Isofol, see http://www.isofolmedical.se/thecompany/history.aspx, a copy of which is attached). Both Biokeys and Isofol are customers of Merck Eprova's drug substance and technology using the herein claimed invention for manufacturing their drug product.

Summarizing the above, Applicants are of the position that at least for their unexpected stability the compounds within the scope of the present application show prominent features and represent a notable progress with respect to the state of the art. Also a person skilled in the art would surely not expect this behavior of the claimed substances and the cited publications do not teach in this direction. The claims of the present application are therefore believed to show compositions with highly unexpected attributes and, therefore, inventiveness over the references.

Reconsideration is respectfully and courteously requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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